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# Matt Ridley

## It's time for the truth. Here's the Covid Paper they don't want you to read

All the evidence on the Wuhan lab leak, properly organised



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Matt Ridley

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Although the world has largely moved on from Covid-19, a lot of trust was destroyed including – unfortunately and worryingly – in science itself. I can think of few things worse for progress than for the public to lose faith in science, which is why I've made it something of a personal mission to get to the bottom of the origin of Covid-19. We need to rescue science's mission of

seeking the truth at all costs, even when it comes with an uncomfortable lesson about the dangers of irresponsible experiments.

As readers may know, I began by thinking a lab leak was unlikely, even impossible, as the source of the virus that emerged suddenly in Wuhan at the end of 2019. But during the late spring of 2020 I saw evidence that this hypothesis was in fact quite plausible and needed investigating at the very least. I teamed up with the molecular biologist Alina Chan to write *Viral*, our book about the search for evidence on both sides of that question. I remained unsure what happened at that stage. Then in the autumn of 2021 more startling evidence emerged to support the lab leak. I now think that is by far the most likely explanation.

Yet still the scientific establishment refused to take the hypothesis seriously, let alone investigate it. There are over 20 million people dead, and you don't want to know why? Imagine if this were their reaction to a chemical spill that killed thousands of people, or a nuclear accident that killed tens of thousands. This killed millions. I tried to get the Royal Society and The Academy of Medical Sciences to debate it, but they refused: too controversial, they said!

Journals like *Nature* and *Science* barely touched the topic and even then only to dismiss the lab leak in condescending tones without bothering to engage with the evidence. Science journalists steered clear of the biggest story of their careers lest it annoy their sources. Yet the public, the world's governments, and the intelligence community all soon came to the conclusion that a lab leak probably did cause the Wuhan outbreak. I found this institutional ostrich act by Big Science deeply disturbing.

In 2024 I was approached by a single member of the editorial board of a respected biological journal with a request that I team up with a British biologist with relevant expertise and compose an academic paper setting out the case for the lab leak hypothesis: he hoped the journal would consider it. With the help of Anton van der Merwe of Oxford University, and advice from Alina Chan, I drafted such a paper. The paper was rejected; I suspect that it was another case of not wanting to rock the scientific boat.

Now I am posting this paper online for all to read. It was composed several months ago so one or two small new items may be missing, but nothing in it has proved wrong. It is written not in my normal style but in dry, scientific prose, with each statement backed up by a source, in the shape of nearly 100

end-note references, so that readers can check for themselves that we have represented the sources faithfully. It deserves to be available to people to read.

Matt Ridley

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Distance from Wuhan to the suspected Covid origins



## The preponderance of evidence suggests that the Covid-19 pandemic began as a result of a research accident

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### Summary

While attempts to identify a seafood market in Wuhan as the source of Covid-19 have failed to find proof, there is growing realization that the source might be the Wuhan Institute of Virology (WIV). In the period up to 2019, the WIV, in collaboration with EcoHealth Alliance (EHA) and other institutions, brought to Wuhan numerous bat viruses from the distant regions where viruses most similar to SARS-CoV-2 have been identified. They created genetically modified versions of viruses and tested them by infecting human cells and humanised mice, causing significant gains in infectivity and lethality in one known case. They did some of these experiments at inappropriately low safety levels.

Latterly they extended the work to include viruses more distantly related to SARS-CoV itself and were party to a plan to insert a furin cleavage site into a sarbecovirus for the first time. There is compelling evidence that the furin cleavage site was acquired by SARS-CoV-2 just before the outbreak. Around the time the Covid outbreak began, WIV closed its database and withheld key information about virus sequences and experiments. These facts amount to a strong though circumstantial case for suspecting that a laboratory leak started the pandemic.

## Introduction

Covid-19, caused by SARS-CoV-2, was responsible for tens of millions of deaths and widespread suffering throughout the world. Yet unlike most outbreaks of novel viral diseases, including SARS, MERS, Nipah and Hendra, there is no consensus, let alone certainty, on how it started. While this is not unique – Ebola and hepatitis C have also proved difficult to trace<sup>[1]</sup> – it is more surprising in an era of sophisticated genetic technology.

The possibility that the outbreak began with a research-related accident was dismissed out of hand by a widely cited paper<sup>[2]</sup>, which concluded: “we do not believe that any type of laboratory-based scenario is plausible”. At the time there was insufficient data to support or dismiss such a claim. The World Health Organisation has since stated that “all hypotheses remain on the table”<sup>[3]</sup> and a letter to *Science* in 2021 from 18 virologists argued that “theories of accidental release from a lab and zoonotic spillover both remain viable.”<sup>[4]</sup> More recently, Anthony Fauci and Francis Collins from the US National Institutes of Health have conceded that a laboratory accident is a credible, although unproven, hypothesis.

Limited cooperation and transparency from Chinese scientists and government have made it impossible to know for sure what happened. Extensive evidence has nonetheless emerged and in this paper we argue that this evidence now points strongly, though not conclusively, to a research related origin for the pandemic, and specifically to a laboratory accident.

## The increasing probability of laboratory leaks

In the past novel human infections came from spillovers from animals that occur all the time. Those that adapted well to transmission between human beings went on to cause epidemics and pandemics. With the microbial revolution of the late 19<sup>th</sup> century and the isolation of bacteria and viruses, laboratory leaks began to happen immediately. With the gene cloning



revolution starting in the 1970s and the massive recent build-up of virology laboratories post the HIV pandemic and again post the SARS and MERS epidemics, laboratory leaks become more plausible. Therefore, it is not clear that natural zoonosis can be regarded as the default assumption or given the benefit of the doubt. Examples of viruses spilling over from laboratories include:

1977 Russian flu H1N1. A strain of influenza extinct in the wild was used to make an experimental vaccine in northern China and caused a global pandemic<sup>[5]</sup>. The virus then became seasonal influenza and circulated up to 2009, killing millions.

2003-4. SARS. Researchers in Taiwan, Singapore and Beijing were infected with SARS during experiments<sup>[6]</sup>.

2007. Foot and mouth disease. An outbreak of foot and mouth virus in cattle was traced to a leak at a nearby virology laboratory in Pirbright, Surrey<sup>[7]</sup>.

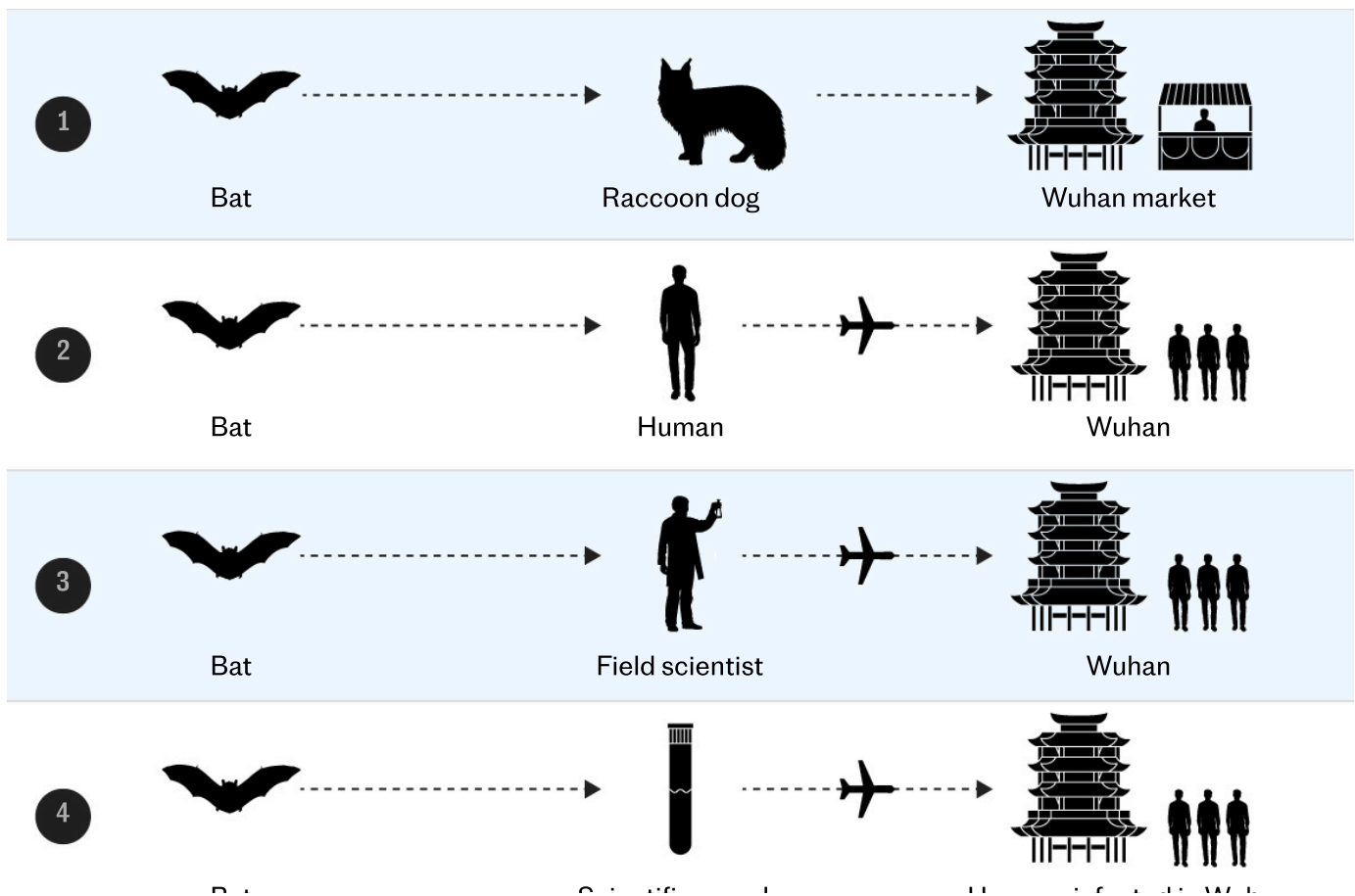
2019. Avian influenza. A researcher was infected during a laboratory accident in Madison, Wisconsin<sup>[8]</sup>.

2021. Covid. Researchers were infected with SARS-CoV-2 in laboratories in Taipei and Beijing, and probably elsewhere<sup>[9]</sup>.

In the United States alone in a four-year period more than 1,100 laboratory incidents that posed significant or bioterror risks were reported to federal regulators<sup>[10]</sup>.

## **Four possible infection routes**

## How Covid spread from bats to Wuhan



Epidemiological and phylogenetic evidence indicates that the first human case of Covid-19 occurred in Wuhan sometime in the last four months of 2019<sup>[11]</sup>. However, the likely animal reservoir of the main progenitor of SARS-CoV-2 is not near Wuhan. All sarbecoviruses (SARS-like betacoronaviruses, also known as SARS-related and SARS-like viruses) have been found naturally in bats, and almost entirely in one genus of old-world bats, the horseshoe bats *Rhinolophus*<sup>[12]</sup>. The two closest relatives of SARS-CoV-2 discovered to date were in *R. malayanus* from Laos<sup>[13]</sup> and *R. affinis* from Yunnan<sup>[14]</sup>. These viruses are 96.8 per cent and 96.2 per cent identical to SARS-CoV-2 at the RNA level respectively.

The main uncertainties therefore surround how a bat virus jumped into the human species and reached Wuhan. Ignoring the implausible frozen-food theory, there are four reasonable possibilities:

- Bats infected animals such as raccoon dogs which acted as intermediate hosts and infected human beings when brought to a food market in Wuhan.
- A bat virus infected a human being who travelled to Wuhan.
- A scientist engaged in sampling bats for viruses became infected in the field and travelled to Wuhan.

Scientists brought samples from bats to a laboratory in Wuhan where a virus infected one or more human beings in the course of experiments.

## Route 1. Intermediate mammal in a market



The assumption made by the Wuhan authorities at the start was that, as with SARS in 2002, this outbreak had begun in a food market, in this case the Huanan Seafood Market where some live mammals were illegally on sale<sup>[15]</sup>. Of the human cases in Wuhan with December onset, several had direct links to this market. This led to the decision, taken on 1<sup>st</sup> January 2020, to close the market<sup>[16]</sup>.

In January 457 samples were taken from 18 species of animal collected in the market, including stray mammals. Virus was detected in none of them but was present in 73 of 923 environmental samples taken from inanimate objects in the market<sup>[17]</sup>. More than 80,000 animals were sampled throughout China in the early months of 2020 without a single case of Covid-19 or antibodies to it being found in other markets, on farms, in the supply chains of markets or in wildlife. Liu and colleagues showed that virus RNA was found at just one wildlife stall out of nine, compared with two out of eight vegetable stalls, five out of 36 livestock stalls, six out of 56 seafood stalls, eight out of 37 poultry stalls, 13 out of 73 aquatic product stalls and 16 out of 87 cold-chain product stalls: so the virus was joint least associated with wildlife stalls and no wildlife vendor tested positive<sup>[18]</sup>. These results led the head of China's CDC, to announce on 26 May 2020 that he considered the market to be the site of a secondary human outbreak, rather than the original spillover: "at first we assumed that the seafood market had the virus but now the market is more like the victim."<sup>[19]</sup>

In sharp contrast to SARS, therefore, Covid left none of the tell-tale signs of a typical food-chain zoonosis: no infected animals, no infected vendors or handlers of plausible intermediate hosts, no ancestral strain in animals, no antibodies in human beings or other species in the wildlife trade, no cases in the supply chain. For a highly infectious virus this is surprising.

## The pangolin episode

On 7 February 2020, the South China Agricultural University in Guangdong announced that a small number of previously confiscated pangolins from the illegal wildlife trade were infected with a virus 98.6 per cent similar to SARS-CoV-2 in the receptor binding domain of its spike gene<sup>[20]</sup>. A second set of pangolin viruses from Guangxi was later published. However, when the full sequences were published a few weeks later it became clear the pangolin viruses could not be the progenitors of SARS-CoV-2 for several reasons:

They were only 90 per cent similar to SARS-CoV-2 overall.

They lacked the characteristic furin cleavage site in the spike gene.

No pangolins were on sale in the Huanan market.

As one evolutionary biologist stated in an email on 21 February 2020:

“Unfortunately, the newly available pangolin sequences do not elucidate the origin of SARS-CoV-2 or refute a lab origin”<sup>[21]</sup>.



The Wuhan Hygiene Emergency Response Team leaving the closed Huanan Seafood Wholesale Market in the city of Wuhan, 2020 Credit: Noel Celis/AFP

## The market as possible epicentre

A 2022 study<sup>[22]</sup> revived the claim that the outbreak began in the seafood market by analysing the distribution of 155 Covid cases out of 174 recorded as having an onset in December 2019 and which were reported to the WHO<sup>[23]</sup>. They showed that those cases not linked to the market lived on average closer to the market than those who had visited the market. Furthermore, the



positive environmental samples, though not the early human cases, were concentrated partly in those parts of the market that were selling live mammals.

However, these conclusions have been challenged on a number of points<sup>[24]</sup>:

At least another 83 December cases had been omitted from the WHO data used in the paper<sup>[25]</sup>, as well as the nine November cases reported in the South China Morning Post on 13 March 2020<sup>[26]</sup>.

The statistical methods used in Worobey et al may not be adequate to support the paper's conclusions. Using their technique, "it is nearly impossible to exclusively identify only the Seafood Market as the geometrical center, while excluding other places in its proximity."<sup>[27]</sup>

Numerous estimates based on phylogenetic analysis suggest a much earlier date than December or even November for the first human infection: "late September"<sup>[28]</sup>; "August"<sup>[29]</sup>; "between July and November"<sup>[30]</sup>; "early October to mid-November"<sup>[31]</sup>; "late October"<sup>[32]</sup>; "the end of September—beginning of October"<sup>[33]</sup>.

Ascertainment bias could explain the centring of cases on the market<sup>[34]</sup>. The Wuhan Municipal Health Commission issued guidelines to physicians for diagnosing the new disease in January 2020. Under the "inclusion-exclusion criteria" a patient had to have had a link to the Huanan Seafood Market to be treated as having Covid, or to be undergoing treatment in one of the hospitals close to the market<sup>[35]</sup>. The head of China's CDC acknowledged in a BBC interview that by looking mainly around the market investigators may have missed cases in other parts of Wuhan.

As for the concentration of environmental samples near the mammal section of the market, this could also be explained by ascertainment bias: "shops selling wildlife as well as shops linked to early cases were prioritised for sampling"<sup>[36]</sup>.

## The double spillover hypothesis

Another 2022 study<sup>[37]</sup> argued that the presence of two strains of the virus, one of which (B) predominated in the market, and the other of which (A) was present on a single glove, could be best explained by two separate animal spillovers, rather than by two human cases in the market, despite the two strains being only two nucleotides apart in sequence. However, this paper was also challenged:

Post-publication peer review comments identified coding errors in this analysis, which significantly reduced the Bayes factors, shrinking the odds of a double spillover, and resulted in the publication of an erratum<sup>[38]</sup>.

The study excluded intermediate sequences from consideration on the grounds that they were caused by sequencing errors, but this has been disputed<sup>[39]</sup>.

The phylogeny of intermediate strains strongly indicated that all known pandemic cases stem from a single introduction to the human species<sup>[40]</sup>.

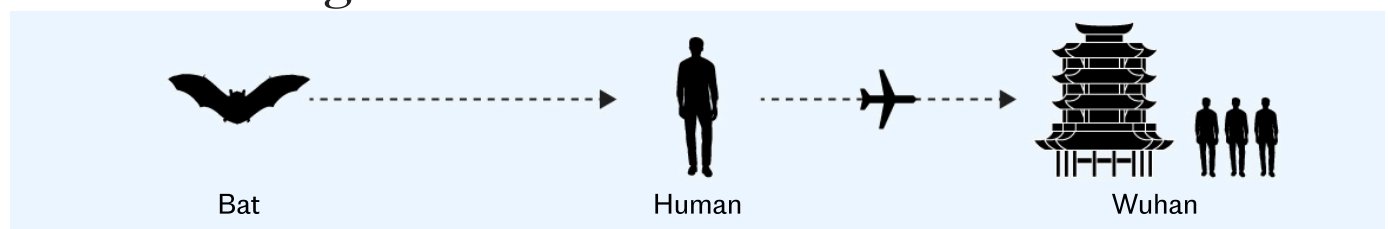
A data set that had been deleted from the NIH's Sequence Read Archive, which included SARS-CoV-2 sequences from early in the epidemic, was recovered. Some of these sequences were closer to bat virus sequences than any from the market, supporting the argument that "the Huanan Seafood Market sequences are not fully representative of the viruses in Wuhan early in the epidemic"<sup>[41]</sup>.

## The raccoon dog theory

In a 2023 leak of data from a paper in press<sup>[42]</sup> was reported to include a sample from the market that contained both virus RNA and raccoon dog DNA<sup>[43]</sup>. Only approximately nine raccoon dogs per week were sold in all of Wuhan's markets. Raccoon dog DNA was present at significant levels in 14 samples from the Huanan market and only one of these had virus RNA<sup>[44]</sup>. In that one, just a single read out of 210 million in the sample was viral genetic material. There was therefore a negative correlation between raccoon dog and virus in the samples from the market. By contrast there was a positive correlation between human DNA and virus RNA.

In short, there is no evidence that the pandemic began with an infected animal in the seafood market. For it to do so without affecting any other one of the tens of thousands of markets in China, or any of the wildlife farms supplying such markets, and without leaving any trace in the animals in the market or among relevant vendors and food handlers, is improbable.

## Route 2. Villager infected in the wild



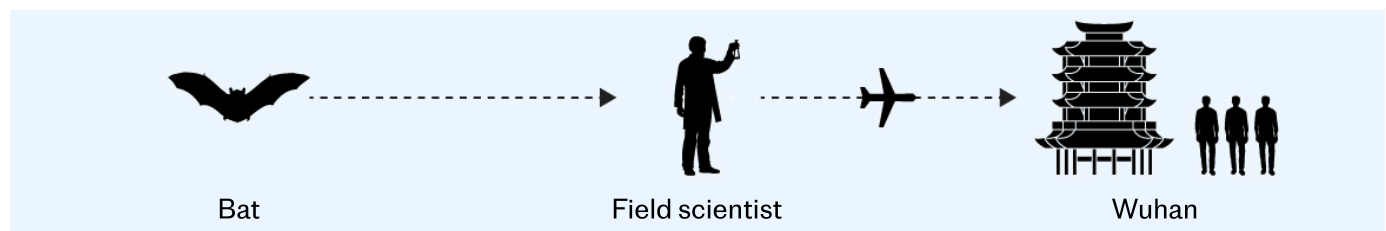
A second possibility is that a human being acquired the virus when visiting a bat cave either as a tourist or while harvesting bat guano. Close relatives of SARS-CoV-2 were found only in Yunnan and Laos, more than a thousand kilometres from Wuhan. In 2015 a study took blood samples from 139 women and 79 men living in four villages close to two caves in Yunnan where sarbecoviruses had been sampled from bats<sup>[45]</sup>. The team also took blood samples from 240 people in Wuhan as a control. Of 218 villagers, six had antibodies to a SARS antigen, compared with none of the Wuhan citizens. This suggests that natural infection from bats may be possible but is relatively rare.

A second, larger study also concluded that “bat coronavirus spillover is a rare event”<sup>[46]</sup>.

Only one possible case of sarbecovirus infection directly caught from a bat is known. In 2012 six men shovelling bat guano in a mineshaft in Mojiang County, Yunnan, fell ill with pneumonia and three died in hospital in Kunming<sup>[47]</sup>. Three separate investigations into their deaths concluded that they had probably caught a bat virus, two of which suspected a sarbecovirus<sup>[48]</sup>. No human-to-human infections resulted from this episode.

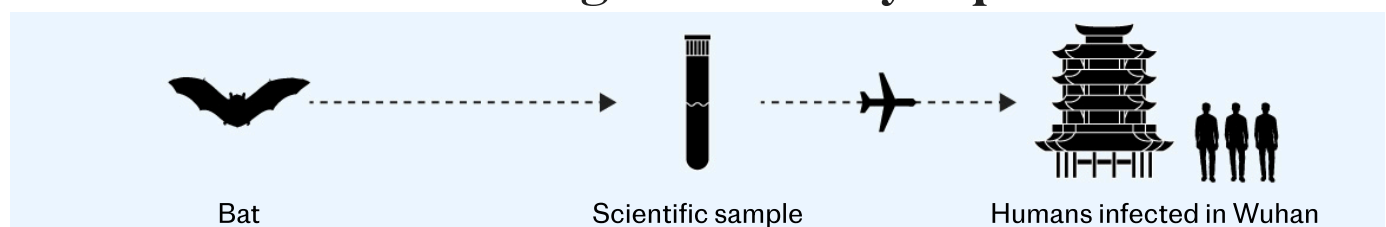
A villager contracting a highly transmissible virus from a bat in Yunnan, not causing an outbreak in his home area, travelling to Wuhan (and not any of hundreds of other cities) and not causing any outbreak along the way, then starting a pandemic only in the city amounts to an unlikely combination of events.

### Route 3. Scientist infected in the field



The Wuhan Institute of Virology led the effort to locate the source of the SARS virus that caused the 2002-3 epidemic<sup>[49]</sup>. In 2017 they announced that they had located a colony of *Rhinolophus* bats in Yunnan which yielded 15 virus genomes closely related to SARS<sup>[50]</sup>. These and other expeditions have increased the risk to scientists in the field of infection by bats. Between 2004 and 2019 Tian Junhua of the Wuhan Centers for Disease Control surveyed 10,000 bats in Hubei province and found no SARS-like viruses but spoke about isolating himself after accidentally coming into contact with bat urine during one sampling trip<sup>[51]</sup>. Full protective gear was worn on some occasions, but a journalist recorded an occasion on which he accompanied an EcoHealth Alliance team into a bat cave in Guangdong without wearing a mask and when he questioned this being told: “I guess it’s like not wearing a seatbelt.”<sup>[52]</sup>

### Route 4. Infection during a laboratory experiment



The fourth possibility is that a sample was brought back to a laboratory in Wuhan and leaked a virus during experiments in the laboratory. Thousands of samples were taken by scientists from bat caves in southern Yunnan, Laos and other southeast Asian countries to the city of Wuhan and to the Wuhan Institute of Virology in particular<sup>[53]</sup>, where they were subject to laboratory experiments.

One notable feature of SARS-CoV-2 was its ability to transmit from human to human from the moment it was detected in December 2019. The scientific consensus, even among natural-origin proponents, is that the virus was well adapted for human transmission<sup>[54]</sup>. According to one study, “evolutionary adaptation within humans was not needed for SARS-CoV-2 to spread”<sup>[55]</sup>. Of course, further evolutionary adaptation continued to occur after the pandemic began and millions of Covid-19 infections occurred every year. But the well adapted, highly infectious nature of the virus at the start contrasts with other zoonoses and is compatible with SARS-CoV-2 possibly having been grown in human cells, monkey cells and/or humanised mice in a laboratory before being transmitted to humans.

In addition to identifying and sequencing the genomes of viruses sampled from bats, the Wuhan Institute of Virology<sup>[56]</sup> reported gain-of-function experiments that created eight recombinant viruses in which spike genes from novel samples were combined with the backbone from a live virus previously isolated from a bat sample (WIV1). Two of these recombinant viruses proved capable of infecting human (HeLa) cells.

In a report to the National Institute for Allergy and Infectious Disease, EHA revealed details of further experiments done in Wuhan<sup>[57]</sup>. In one, three chimeras with spikes from one virus and backbones from another caused up to 10,000-fold higher viral loads in the lungs of hACE2-transgenic mice compared with control infections. One of the chimeras (WIV1-SHC014S) also caused greater weight loss and mortality in the mice.

## **WIV’s unpublished viruses**

These results involved viruses closely related to SARS. A common argument made against the lab-leak hypothesis is that the WIV did not possess SARS-CoV-2 or a 98-99 per cent similar virus to use as a backbone before the pandemic. However, there is disagreement on this point. One paper emphasised that “SARS-CoV-2 is not derived from any previously used virus backbone”<sup>[58]</sup> and another argued that there is “no rational experimental



reason why a new genetic system would be developed using an unknown and unpublished virus”<sup>[59]</sup> but one of the authors of both papers, Robert Garry, said in a private message: “you would NOT use an existing close [clone] of SARS or MERsV. These viruses are already human pathogens. What you would do is close [clone?] a bat virus th[at] had not yet emerged.”<sup>[60]</sup>

Peter Daszak of the EcoHealth Alliance repeatedly claimed to know all of the viruses possessed by the WIV. However, he admitted in congressional testimony (June 2024) that his comprehensive summary paper<sup>[61]</sup> included only those viruses sampled before the end of 2015 and he was unaware of all the samples WIV was continuing to collect after that date. In a grant application for the period up to 2019, referring to the work of its subcontractor, the WIV, the EHA stated: “We aim to expand the known diversity of SARS-CoVs by over 125 strains.” Edward Holmes wrote to David Morens at NIH in September 2021 that “I’m pretty certain that groups in China are sitting on more SC2-like viruses”<sup>[62]</sup>.

This is underlined by the fact that the WIV’s bat and rodent pathogen database, with a password-protected section for unpublished viruses, was made inaccessible to outside access on 12 September 2019<sup>[63]</sup>, prior to the outbreak, and has never been accessible since. Given that sharing this database could instantly prove the lack of a progenitor virus to SARS-CoV-2 if it does not contain such a virus, this failure to share data must be taken into account.

## **WIV’s possession of the closest relatives to SARS-CoV-2 at the time of the outbreak**

The history of one particular virus illustrates the difficulty of knowing what viruses were in the WIV’s possession. Following the Mojiang mineshaft episode, the Wuhan Institute of Virology mounted at least seven expeditions to the site (a distance of 1800km by road) over two years to sample bats<sup>[64]</sup>. In 2017 and 2018, the WIV began to sequence the genome of one virus from these samples. This virus, known as Ra4991 in a master’s thesis<sup>[65]</sup>, was significantly different from those found elsewhere but later would prove to be very similar (96.2%) to SARS-CoV-2. Its sequence was not published until January 2020 when it was renamed RaTG13<sup>[66]</sup> without the renaming being mentioned, leading to weeks of confusion until March 2020<sup>[67]</sup>.

It later turned out that eight other viruses closely related to SARS-CoV-2 and Ra4991/TG13 with serial numbers beginning with 7896 were also collected in

Mojiang<sup>[68]</sup>. The existence of this group of viruses was confirmed in 2020 by a WIV thesis submitted in June 2019<sup>[69]</sup>, which came to light only in May 2021. This thesis placed the nine Mojiang viruses in a new group within the sarbecoviruses known as “Lineage 4”. Yet when the same work was published in 2019<sup>[70]</sup>, the Lineage 4 viruses were omitted from the paper and its charts.



Security personnel keep watch outside the Wuhan Institute of Virology during the visit by the World Health Organization (WHO) team tasked with investigating the origins of the coronavirus disease (COVID-19), February 3, 2021 Credit: Thomas Peter/Reuters

## WIV's and EHA's intended work on novel sarbecoviruses

An EHA grant renewal application to NIH in November 2018 (R01AI110964), stated: “We aim to expand the known diversity of SARS-CoVs by over 125 strains, targeting 10-25% S protein divergence that we predict infers high spillover risk and evasion of immune therapeutic and vaccine efficacy.” Peter Daszak of EHA told an interviewer in 2019 that “the logical progression for vaccines is — if you’re going to develop a vaccine for SARS, people are going to use pandemic SARS, but let’s try and insert some of these other related [spikes] and get a better vaccine.”<sup>[71]</sup> The viruses from Mojiang would have fit this description, one of them, Ra4991/TG13, being approximately 25% divergent in the spike gene<sup>[72]</sup>. This may explain the renewed interest in sequencing them in 2017 and 2018.

However, another group of SARS-CoV-2-like viruses was discovered in 2020 in Laos<sup>[73]</sup>, one of which, BANAL-20-52, is even closer than Ra4991/TG13 to

SARS-CoV-2 in sequence: 96.8%. It is not sufficiently close to be the progenitor itself, however, and in any case EHA was actively sampling viruses in Laos and sending them across the Chinese border to Wuhan during this period<sup>[74]</sup>. The horseshoe bat species from which the virus was derived, *R. malayanus*, also yielded another SARS-CoV-2-like virus, RmYN02, in Mengla County, Yunnan, just north of the Laos border<sup>[75]</sup>.

## The DEFUSE proposal

In March 2018, the EcoHealth Alliance, in collaboration with the Wuhan Institute of Virology and two other institutions, applied for \$14 million to the Defense Advanced Research Projects Agency (DARPA)<sup>[76]</sup>. Called DEFUSE, this was a plan to continue the work of identifying new sarbecoviruses, experimenting with the creation of chimeras to test pandemic potential, and work towards creating vaccines to protect troops against bat-borne infections during combat. When the pandemic began, the applicants chose not to reveal the existence of this document, which was leaked to the media in September 2021<sup>[77]</sup>.

The DEFUSE proposal was turned down by DARPA. However, the work described in it may have already started, and may have continued using other funding. A Chinese Academy of Sciences “special project” on similar topics was launched in 2018<sup>[78]</sup>. A grant was issued to WIV the same year to study “pathogenicity of two new bat SARS-related coronaviruses to transgenic mice expressing human ACE2 receptor.”<sup>[79]</sup>

## The furin cleavage site, unique in sarbecoviruses

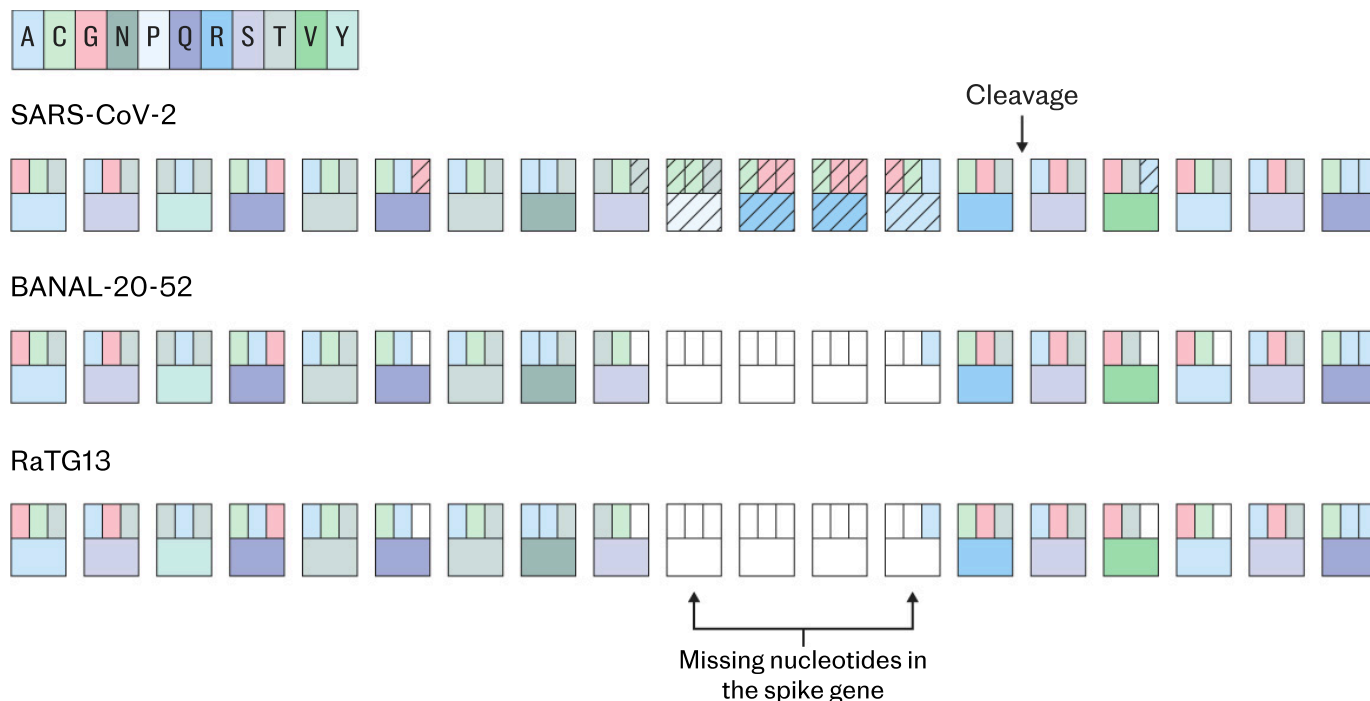
DEFUSE revealed an ambition to insert furin cleavage sites into sarbecoviruses for the first time. The key sentence read as follows: “We will introduce appropriate human-specific cleavage sites and evaluate growth potential in Vero-E6 cells and HAE [human airway epithelial] cultures.” The DEFUSE proposal makes clear in early drafts that they were interested in FCSs at the S1/S2 boundary of the spike gene.

Some viruses have the ability to use a cellular enzyme called furin to cleave their spike proteins, enhancing their ability to infect other cells. MERS has this ability, SARS does not. SARS-CoV-2 is the only sarbecovirus that has this trait<sup>[80]</sup>. A furin cleavage site appears to be actively selected against in enteric infections in bats<sup>[81]</sup>.

Comparing SARS-CoV-2 to its closest relatives, it is clear that the furin cleavage site in SARS-CoV-2 is the result of a genetic insertion of 12 nucleotides adjacent to the junction between the S1 and S2 sections of the spike gene (see Figure 1), spelling out an arginine-rich set of codons: PRRAR.

## Genetic makeup of SARS-CoV-2 and it's closest relatives

SARS-CoV-2 has 12 nucleotides that are missing in it's closest relatives



**Figure 1.** *The furin cleavage site insertion in the SARS-CoV-2 spike protein, with codon and amino acid sequence differences from the two closest bat viruses highlighted. Other alignments are possible.*

Several groups of scientists had inserted or manipulated furin cleavage sites in viruses in the 2010s. One study, to which the WIV was a contributor, compared MERS (which has a FCS) with a similar virus HKU4 (which does not) and showed that the introduction of two mutations into HKU4 allowed the virus to use furin to help it enter human embryonic kidney cells<sup>[82]</sup>. In 2019, another study<sup>[83]</sup> showed that in two MERS-like viruses it was “proteolytic activation” through cleavage, as well as receptor binding, that determined which species of animal MERS-like viruses could infect and “offers a means to recover previously unrecoverable zoonotic CoV strains.”

The WIV would have been aware that to get bat sarbecoviruses to grow in human or mouse cells, adding a furin cleavage site could be helpful. Shibo Jiang, of Fudan University, Shanghai, who was a co-author with Shi on the 2015 Minnesota paper, had created a furin cleavage site in a non-viral protein via a 12-nucleotide insertion<sup>[84]</sup>. Jiang was working on sarbecoviruses in 2019.



That the furin cleavage site is a novel feature in SARS-CoV-2 is suggested by a point mutation in the virus, D614G, which appeared first in human beings in early 2020 and quickly became widespread<sup>[85]</sup>. This mutation stabilises the spike protein after cleavage<sup>[86]</sup>, preventing dissociation of the S1 domain and thereby preventing the premature assumption of the S2 domain's post-fusion conformation<sup>[87]</sup>. This suggests that the FCS was introduced into the virus just before the pandemic<sup>[88]</sup>. Given the absence of a FCS in any other sarbecoviruses, the most parsimonious explanation for this is that it was introduced by scientists into a SARS-CoV-2 predecessor being grown in human or monkey cells in culture, as proposed in the DEFUSE proposal.

When the pandemic began in January 2020, Shi Zhengli of the WIV published two articles, one co-authored with Shibo Jiang<sup>[89]</sup>, yet in both of them failed to mention the furin cleavage site, by far the most remarkable feature of the new virus's genome. This may have been an oversight, but by contrast, it was the furin cleavage site that immediately alarmed several western virologists on first seeing the genome of the virus and led to the drafting of the Proximal Origin paper. Messages released during a congressional investigation reveal that the authors of the paper were not themselves convinced that a laboratory origin could be ruled out, either during or after the writing of the paper<sup>[90]</sup>.

## **Work done at low safety levels**

One feature of DEFUSE is especially troubling. In an early draft of the proposal, two of the applicants engaged in a brief discussion of the wisdom of doing certain experiments in Wuhan at Biosafety Level 2. Peter Daszak described this as “highly cost-effective”; Ralph Baric thought it would cause US researchers to “freak out”. In a later exchange of emails after the pandemic began they revisited the issue with Baric writing to Daszak: “You believe this was appropriate containment if you want but don’t expect me to believe it”<sup>[91]</sup>.

## **Conclusion**

In only one city in the world were sarbecoviruses subject to gain-of-function experiments on a large scale involving human airway cells and humanised mice at inappropriate safety levels: Wuhan. At only one time in history was research to create novel sarbecoviruses with enhanced infectivity through furin cleavage under consideration: 2018 onwards. The surprising failure to find better evidence for a natural spillover, and the lack of transparency from the Chinese scientists, is therefore best explained by positing a laboratory

accident involving a live virus experiment as the cause of the Covid pandemic and attempts to cover it up.

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Matt Ridley is the author of *The Rational Optimist: How Prosperity Evolves* and most recently *Birds, Sex and Beauty: The Extraordinary Implications of Charles Darwin's Strangest Idea*.

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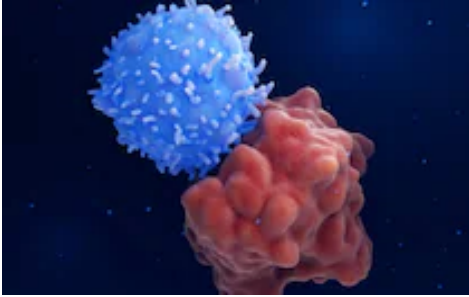
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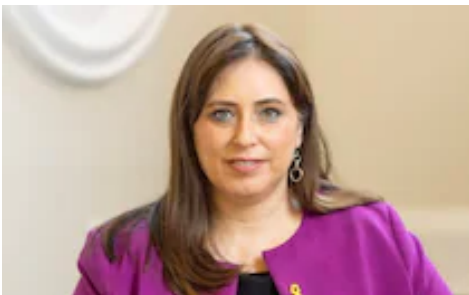
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